18/5/93. Criteria:- interest area; discussion; date of Publication; European.

ETS exposure & fetal health.

Authors of studies which may be interested in working with us:

① Yerushalmy, J. (1971) MSP41-44.

Philosophy interesting – was at Berkeley in 1971 but 22 years old & in States!!

② Comstock, G.W. & Lundin, F.E. 1967 – Bethesda. MSP41-46.

Too old!!

Call from Richard Cochran:-

End of June – Pesticides – to meet people Frankfurt
ingredients & regulatory & pesticide.

Toxicology.

Longer term understanding of regulatory environment.

⇒ HCL / Boden connection

Meeting in Oslo – should I AM go? –

Javier Braña: Spain.-

CIA director

Tito Valenzuela

AREITIO, Javier.

③ MacArthur, C. & Knox, E.G. 1987: Dpt of Social Medicine, Birmingham.

Suggest in their paper that there may be other factors associated with birth weight which are not established in most studies.

2028541625

24/5/93.

1) Ref - [illegible] etc. + photocopying
2) Write [illegible]
3) Check ref [illegible] for strains - order what needed [illegible]
4) Check [illegible] book & Ecobichon & Wu (Also for childhood [illegible]).
5) Sort out [illegible] consultant group
6) "Report" [illegible]
7) Spanish [illegible]
8) [illegible] [illegible] of [illegible]
9) Gorrod [illegible] [illegible] through

Check all reviews - NRC EPA RSP etcetc....

25/5/93

① HSR - response re nicotine/blood cotinine ubiquity' - Feb 5th SHB report.
② See PEH re Gorrod.

25/5/93.

Nicotine in plasma.

1). For information on DeBethizy's report Oranity McDonald. etc.
2) Ask Rosemary to do search for further publications this year from MD. James Pirkle. & Mrs Margarita Haglund.
3) Look up any articles which may estimate dietary contribution of nicotine to blood cotinine levels - estimating ± cases.

2028541626

Possible dietary sources of nicotine: -

Tunstall-Pedoe etal, 1991. p1412. Table 7.

Median serum cotinine levels in "Non-exposed" tea drinkers 0·32 ng/ml.

CDC paper reports levels as low as 0·030 ng/ml.

Hale, 1990. p 314. dietary could contribute equiv to 1-2 cigs....

Castro & Manji etal. RAB - 50-100 ng/ml. nic in blood fr diet.

Tuesday p.m.

① Write up Nicotine/cotinine levels in blood from dietary sources comments.

Comments on claim that ETS exposure in "ubiquitous".

This claim is based on an article in MMWR, 42(3) 1993 reporting on preliminary results of the third National Health and Nutritional Examination Survey, (NHANES III) - specifically findings of serum cotinine levels in 800 ~~children~~ individuals.
This study ~~has measured~~ used a technique sensitive enough to measure as serum cotinine at 0·03 ng/ml. and found that all 800 individuals measured between @ 4-91 years shared some level between 0030 - 650 ng/ml.
Unfortunately there are no data presented and insufficient details on the spread to comment on the significance of this finding. At levels as low as 0·03 ng/ml, however, the contribution of dietary nicotine supply has to be considered. Below several literature references are used to demonstrate that levels of 0·03 ng/ml and up even 10× these levels are quite feasibly entirely representative of dietary sources. It is therefore not in the least bit surprising that all 800 individuals shared some serum cotinine and is not at all, as claimed, indicative of ubiquitous ETS exposure to tobacco smoke.

2028541627

Up until this NMWR report the sensitivity of serum cotinine measurements was not sufficient to detect levels as low as 0.03 ng/ml ~~therefore~~ however ~~by~~ using in several papers dietary contribution has lead to levels orders of magnitude higher than this....

The dietary sources of nicotine have been discussed in several papers: (refs 1-4).

in 1986, Castro & Mayi ~~suggested~~ calculated that ~~availability of nicotine from~~ dietary tomatos, ~~as~~ peppers and eggplants (aubergines) could supply nicotine at levels similar or even in excess of ~~a~~ "low-yield" cigarettes.

in 1990 a review of ~~potential~~ the nicotine in tea from Tunstall-Pedoe et al reported median serum cotinine levels increasing from 0.01 ng/ml in non-tea drinkers to a 0.32 ng/ml in drinkers of 8 cups of day. ~~Even then non-tea drinkers were unable to measure levels lower than this~~ This implies even one cup of tea a day, alone, would contribute to ~~the~~ the 0.03 ng/ml found in NMWR.

In 1990 a review by Idle calculated that a reasonable dietary contribution would be in the order of the equivalent of 1-2 cigarettes per day.

Finally in 1991, Dawn et al calculated that if ~~only~~ average quantities of ~~the most common~~ any a few nicotine containing vegetables, (Tomato, Potato, Cauliflower & Black tea) are taken the daily intake of nicotine would be 8.8 µg ~~or~~ going up to a level of 99.9 µg daily on ~~the~~ in larger intake, this alone being equivalent to one of the ultra-low cigs now available.

It can thus be seen that at the very low levels mentioned in the NMWR report dietary sources of nicotine are at least significant if not the only source of ~~nicotine~~ environmental. This data does not, therefore ~~have any~~ suggest that ETS is ubiquitous - merely that nicotine is!

Reporting on Witpreg2

1). For Ref list only -

Sort Author Alphabetically

Col. 1. Col. 2 Col 3. (Col 4)

Author. Date. Journal. (Code)

To perform: - Open Witpreg2: Select Sort Records - Author Alph.
Make "Author" bold: Make "Journal" "Italic"
? - <> "ETS not Investigated" in Result column.
OPTIONS Press F5 - "Goto" box =
~~Add Title~~ -

Add title in WDP report Mode: - View: Create New Report etc = (p 317).

For Main Report

Sort as follows:-

Author ; Endpoint; Results.

but breaks in as appropriate: -

Thursday 27th May 1993.

1) Phone Call from Gerard Wirz re IARC - EPA in Europe?
- Only if they perform an "evaluation" on ETS which we have no evidence of at the moment.
Also visiting Tuesday for discussions with PEM/HSE.
Interested in classification of carcinogens - RHS list for European classification Risk assessment etc.....

2028541629

Weetman book ⇒ Spain? W

28/5/93

PEM: Files from Peter to sort through. (Eng.

Weetmans Nos: - Eng 914 154051 (home?) } Look through paper of Carcin-
Work 915 152603 (work) } Check budget position see HER ring Max Weetman

TAC position paper on monitoring w PEM ⇒ file copy TAC file.

Nilsen. - Send abstract from Mizuno extr/v intrinsic from Infofo.

- File all papers on NIC in Hair - occasional check w Rosemary
- PN Lee talking in TAC about it - ADA asked for summary paper
- Call Tony for his response on these papers.
- Call Odd with comments on papers

Conrad follow up: . . . . .

Meeting 1/6

Questionnaire - classification carcinogen lists - check R45
for IARC

Draft on SIDS for Denmark - written response

to confirm

ADC
4-02
1-30
1-34

40p/mins expand

Gerard Wirz
9.12 010 32 2 287 8011
9.16
9.17 IGG - 10.30 11.00 Whitpole st.
David Turato 5x40p - £2-00. Switzerland

2x40 = £1-20

10-00
10-02 ①. List of carcinogens Sharon Spanner [redacted] SUAC. ⇒ HER + 25 min 10.02
10-42 ② Questionnaires
10-43 ③ PM-USA - Junk Science brother PM-USA Response to EPA
25 mins

25 x 4 = 100

2028541630

3/6/93. IGG.

Report on Melbourne meeting.

Assays which for more than one guideline has been published & previously conflicts discussed

Key resolutions :- D. KIRKLAND - MAIN SUBGROUPS

1) Solvent -ve controls - as long as historically solvent doesn't have effect solvent control alone is fine (N.B. contra latest U.S. Red book')

2) In vitro Assays a) top dose - 5mg/ml or 10mM (whichever is lower) - but higher or lower may be justified.

b) Metabolic Act :- post-mitochondrial fraction fr rodent liver induced either by Aroclor 1254 or phenobarb/β-naphthoflavone (not equivalent but equally acceptable)

c) solubility :- determine in test medium - may change during exposure.

d) precipitates: caused a lot of problems Japanese data suggest 31/770 (4%) chemicals only positive w precipitate range (candidate data) compromise - highest dose should be lowest insoluble conc.

e) positive controls :- no specific advice - mutually acceptable alternatives left to the experimenter = no consensus

3) In vivo Assays a) vehicles - PBS/ water were possible : would avoid to exclude oil.

b) animals young adult sex mature rodents.

c) limit doses - 2000mg/kg/d. up to 14days >14d 1000mg/k/d.

d) dose levels - if limit dose, use that dose only. If toxic use 3 (or 2) dose levels.

e) MTD. - clear clinical signs or fraction of lethal dose mutual acceptance of alternative arrangements:

—//—

WORKING GROUPS

BACTERIA - Dave Gatehouse - debates most on strain TA98, 1535 100 1537 etc. 1537, 97 97a interchangeable. E coli or TA102 routine.

(OECD/EPA EC UK DOH MHW/MOL MAFF & CANADA)

test systems - preincubn - insufficient data to make recommendation!

~~test repetition~~ → * No agreement on evaluation of results can use stats but don't have to!

CYTOGENETICS David Kirkland.

Cytotoxicity - MI can be misleading - measure survival.

top dose - interesting debate - above 50% cytotoxicity no valuable info gained ∴ top dose should be greater that 50% - but no need to go higher.

2028541631

serum - no agreement +/-

Metab activn 1-10% S9 in medium

dose levels - should be closely spaced

test repetition - majority vote - no need to repeat positive but should repeat negative? - all except one agreed that there was no need to repeat clear negatives.

replication majority vote no need to replicate cultures

polyploidy - assay not designed to detect polyploidy.

Treatment & sampling times = debated. 1.5 NCC (normal cell cycle) sufficient other than for nucleoside analogues & nitrosoureas.

evaluation - use stats if you want.
dose-dependents increase .. etc.

UDS assays Steve Dean. (Dave Doolittle!)

21 Q's - 1) fund answers. - recommend primary hepatocytes but other organs could be justified

2) - Species -- Rats strongly recommended but alts could be justified

Cell mutation Assays Robert Rees.

Main conclusion - Drop Quadrain

- no need for repeat test if negative
- duplicate cultures can be done if it can be justified by a suficient database

NVIVO CYTOGENETICS & MICRONUCLEI. Diana Anderson

Major debate around sexes.

James Mackay — Nike Sabmones data on can oil mail under debate was been asked to 'present' the data & a decision will be made about whether or not it will be suitable for use in mammalian studies after.

DJK. Summary bullet points should be available now (within 1 month)
Publication Internet Board (Augustus)
should go to OECD coordinators to see how the recommendations could be implied.

Jim Bodman: Germ cell assays.

1) Robin Fielder to send out RHS based carcinogen list with directive etc.

N.B. He said that DoH concerned about global ban of all RHS's I was contacting industry about this.

May be worth ringing Robin to find out more about carcinogen classification in Europe.

Boards - European members propose for inclusion boneday

what? - No idea? -

2) Ring DJK find out details of Melbourne meeting & publication plans etc etc

Robin Fielder - recommendations of U.K. to OECD. Updating of 471 & 473 etc.

SRE transformation rejected.

UDS in liver in vivo - supported.

Updating of existing guidelines - 471 (Salmonella)

474 - Bone marrow MN 473 in vitro manual cytogenetics.

476 - Gene mutn

Biggest debate seems to be over repeating clear negatives.

and some debate on in vivo sex selection.

OECD consultation meeting 30 Nov - 2 Dec. FDA - London

w objective to achieve consensus on & technical content of the updated & new genotox. guidelines

Now 2nd circulation - may go to full working group or straightforward acceptance

London meeting v Melbourne - large amount of consensus.

main exception is repetition of in vitro studies -

More important to design second study to be most likely to pick up another kind of activity - particular UK concern

Basing alert of relevance of in vitro tests ∴ should be repeated but not identical - "improved"

(American PMA data on 680 compounds - always repeated equally)

Dave Turats

International Conference on Harmonisation (of Technical requirements for pharmaceuticals for human use)

FDA, EEC, MHW (Japan); PMA states (Pharmac. Man Assoc. USA)
EFPI. (Europ. fed. Pharm. Ind)
Japan Pharm Man Association

1989. 12 m rodent studies; etc etc. reproductive toxicology guidelines
→ single set of guidelines on reproductive toxicology which is now ~~exist~~ expected after October 1993. & accepted by diff reg auth.

ICH 2 - Oct 26 - 29th - Safety - Carcinogenicity - Rats & Mice
Top dose
when?
[Toxicokinetics - No guidelines up to now.
Genotoxicity -]

Genetic Toxicity issues for harmonisation

1) Strategy issues.

e.g. need for in vitro mammalian mut assays in core ~~or~~ battery
need for E.coli ; timing in rel to clinical trials; minimal battery

Test performances.

validation of results, testing precipitates, repetition of tests etc etc.

(E.coli main agreed necessary to include)

Micronucleus & chromosome abs - suggest effectively interchangeable

Diffs from Melbourne.

- Use of both sexes - if there is no diff in toxicity between ♂ & ♀ rats or mice in toxicity at either single dose or repeat dose up to 14 days then males is acceptable on their own.

Recommendation circulated in March - worldwide revision currently being carried
Japanese particularly concerned about precipitates

What to do with in vitro test results - (use IARC database)

Size.

At send - the box with the list of carcinogens in comparison.

Fa G.P.A. EPA give - Give IK at end.

describe los classifications of cancer A, B, B_2, C, D, E.

Article from Spanish hospital in IARC ...

Dont start with the political -
start with the facts. -

cuimentas - first.

EE UU not representative of Europe

Aresto prefers will presentation more general on the science - on
what is ETS - what are people breathing etc.
more classical Helmut Gaisch presentation.

Data on cigarette equivalents - on hallazgos

Dont explain methods too much ....
explain exactly what EPA has said.
emphasise on key figures.

EPA - es una estudio ......

Fundamental point es el ETS no es un factor de riesgo.

[Comparison of other risks. - in expand ....
con hechos ...]

Kip Viscusi - Smoking: Making the Risky Decision Oxford Uni Press 1992
ISBN 0-19-504486-1

Prepare invitation to J. Rita - to see what we can offer

Seize

2028541636

11th June 1993.

Pfgs clearout -

Check with Helmut re NHANES III news from Bob.

Wkf re seminar ..... arrange .....

HIV & smoking - St Mary's Hospital London. Published soon in "AIDS"

French exam - hols. Monday 21st: 8:30 → 11:15.

13:45 → 15:00

16:40 → 17:00.

(Jdm 16:20? →

—.

Tobacco Smoke and Asthma in Children - Chilmonczyk etal .....

N. Eng. J. Med, 1993: 328; 1665-9

Aim - use urine cotinine levels + parental reports to examine relationship of ETS exposure with pulmonary function measurements and acute exacerbations of asthma.

Method/Design 204 children w asthma (age 9 months to 13 years) and the parents who accompanied them to routine visits ....

⇒ 199 parent/child pairs -

At enrollment parent questionnaire & urine sample from each child.

demographic
occupation
education
household.
age at diagnosis
child's medication
child's school status
day-care
smoking by parents
smoking at day care
smoking in household

145 children - pulmonary function
urine cotinine w quality control standard.

Findings:

1) Agreement with cotinine & questionnaire fairly good

When questionnaire data only is considered only No of exacerbations is dramatically increased. There appears to be some discrepancy w r t

FEV_1 (%) - 109·3 ± 20·7; 102·4 ± 26.0; 102·2 ± 17·9.

FEV_{25-75} (%) 85·4 ± 26·7; 71·8 ± 30·6; 73·6 ± 19·3.

Ratio $\frac{FEV_1}{FVC} \times 100$. 83·7 ± 7·6; 79·4 ± 8·4; 80·0 ± 7·0.

2028541637

When coronine measurements are used the results return random.-

Nº acute exacerb:	2·1 ± 1·9 ;	2·8 ± 1.8 ;	3·6 ± 2·9
FEV_1 (%)	108·8 ± 20·3 ;	105·2 ± 24·7 ;	98·5 ± 22.3
FEF_{25-75} (%)	85·4 ± 26·8 ;	74·9 ± 28·8 ;	67·3 ± 22·8
Ratio FEV_1 to FVC	83·5 ± 7·5 ;	81·2 ± 8·1 ;	77·5 ± 8·0

But note :-

1) The means of measuring Nº of acute exacerbations is not defined.....

"All the childrens medical records were reviewed in a blinded fashion to determine the number of acute exacerbations of asthma during the 12 months before enrolment and to obtain information about use of medications."

2) Figures vary between 2-4 acute exacerbations in 12 months

—H—

Bob Pages:- Thursday - Talk to Tony Andrade

10:30 internal Glaxo broadcast - statement -

June 16th 1998. BECKMAN CONFERENCE....

Markers along scale from exposure to effects.....
Lead - ALA dehydrase could be considered in any one of the categories, (exposure, effect, susceptibility) as it is a measure of exp but is a response (i.e. an effect) to exposure and varies in individuals

New approaches to examine exposures have to be validated.....
Personal habits & Genetic & epigenetic characteristic determine exposure & it is here that biological markers have major contribution to give.
Most notable advances:- DNA, protein adducts.

oriented mutns:- retinoblastoma, colon cancer, breast cancer.
Lead exposure; blood lead, erythrocyte protoporphyrin, ALA
immune response; CD4/CD8 t lymph ratios etc.
very complex - interpretation not always clear.

limits- lack of knowledge of target organ system
" " physiologic response to toxicants.
" " access to biological events.
" " sensitivity / specificity.
Inherent & interindividual variability.

Access - Compartments generally available= urine,
hair
cerebrospinal fluid
seminal fluid / sperm.
skin
saliva
blood - plasma, serum, rbc, ly, pl.

Within the nervous system most of the events which we would like to measure are not accessible - some advancement with e.g. PET scanning but problematic exposure and full potential not yet realized.

One major limit - our understanding of toxicokinetics & distribution & often we are not measuring the compound in the most relevant compartment.

Interindividual variability - the more sensitive methods become the more we should consider the role of interindividual variation

Goals of Biomarker research:-
① Identify markers of early events assoc w exp or response
② Validate predictive capability of markers (backwards to exposure assessment & forwards to disease)

2028541639

These first 2 are the most important goals....
3. Increase understanding of mechanisms of disease toxicology.
4. Improve risk assessment methods
5. Identify specifically sensitive groups } Biomarkers may or may not help in these areas
6. Apply Therapeutic intervention

—

How we cope with exposures (realistic) - to the cocktail of toxins that we are really all exposed to in a remote dream....

Burger Heinzow (Kiel, Germany).

~~Repp~~ Critical Evaluation of Approaches to Exposure Assessment:-

Public fears call for risk & exposure assessment.....
IUPAC definit
~~The retained toluene GA is the qu~~.

Urinary cadmium levels increase in smokers.

Normalisation - creatinine. not always sufficient

—

Eric Sampson
CDC - Atlanta :- "Exposure Marker Methodology: Technical & Scientific Developments.-

Exposure Markers = Internal dose } - Measurement of environmental exposure
Biological effective dose }
Target site

Dioxin, Nicotine & Lead.
Exposure markers for internal dose should show a defined rel. w exp w adverse effects etc.

N.B. Dioxin in only one of 75 congeners
Exposure markers in comparison to indirect measures.
Agent Orange exposure to Dioxin in Vietnam - estimated/calculated exposure index later measurement showed no correlation.
Air force abandoned exposure index.
(WC Fields cigarette quote)...

Urinary cotinine in smokers & non-smokers was clear cut off in cesarian studies - mixed questionnaire data not reliable in intervention group particularly.

Human Pharmacokinetics.

Animals diff from humans - dose differential etc etc.....
Animal half life of dioxin suggested 6-15 wks ∴
but later in humans it was established to have a half-life of approximately 7 years.....

Human sampling

Dioxin in adipose - was thought that adipose was best but later found that serum levels are very closely correlated as long as adjusted for adipose.

Advances in technology

1) Mass spectrocopy analysis of 23,000 serum samples for cotinine. to make sure as accurate as possible
Using liquid chromatography at beginning now can process 100 samples a day

2) Blood samples - was need 2 mls blood where used to need 200 mls

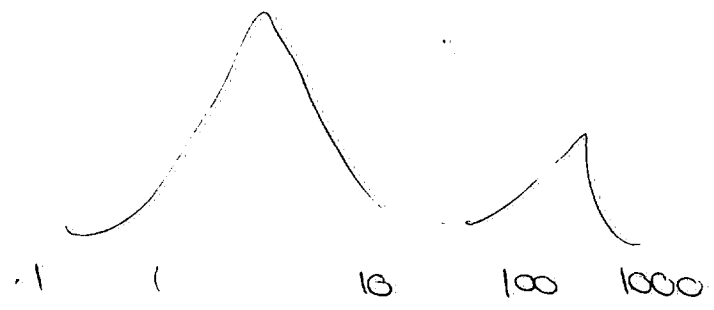
3) Internal standards

4) Clean up - procedure

NHANES III - lead activities correlate w lead in petrol

NHANES III Passive exposure first 9000 people = see cotinine.

0.01 – 15



Serum cotinine ng/ml log scale.

Also pesticides

Interpretation and measurements

Blood measurements - N.B. Background Uruguay.
Missouri Times Beach = Background.

Highest - workers & sewers - follow up should be in higher exp groups.

Conclusion

* Need more human data *

To determine whether these toxicants are causing health effects in people...

Prof Hada - Kyoto University Japan
Because most Japan is continue only Raw Rayon making?

*A. They are investigating other sources - e.g. dietary tea etc....

Lead may be going down but are Palidium & Rhodium going up? -
Not yet being looked up but should be.

? - Should we decide where & when to measure? We need to prioritize the analysis

---

Prof Antero Aitio Finland.

Reference Intervals Validity in Environmental & Occupational Toxicology:

P.M.

METALS: CURRENT CONTROVERSIES.

Joseph Graziano, Columbia University New York.

"Lead: Validity of Exposure Markers in Diagnosis and Surveillance"

Uncertainty of measurement is larger as levels of smaller.
Relationship of Pb in hair - insufficient known to be at all useful

Robert Lauwerys. Louvain.

"Cadmium Exposure Markers as Predictors of Nephrotoxic Risk"

Exposure: Food, Tobacco.
Industrial: dust & fumes.

Absorption = 2-7%
Pulmonary: 25-50% - dust varies much.
Distribution 90% bound to RBC - accumulates in kidney & liver (50%)
Half-life up to 10 years
Metabolism: - Urine, bile, hair etc.....
Toxicity target organs - lung, bone, kidney (= critical organ)
High exposure level in industry - (carcinogenic potential.

Biologic Markers of Exposure.

Direct measures possible but exposure is not restricted to effective dose.
Indirect measures:-
Cd in blood - last few months of exposure only.
Mainly influenced by current exposure and less by the body burden.
Cd in urine - At low exp conditions - before saturation - urine Cd mainly represents the amount stored (ie. body burden)
In NS correlated with oral dairy intake
Cd in hair reflects concentration in anagen phase but difficult to discriminate from external sources

Conclusion Cd in urine = most useful measure

Cadmium induced low molecular weight proteinuria should be considered as an adverse effect. So far no prospective study has been carried out to demonstrate that

Cadmibel - Epidemiological study of 2327 non-occup exposed subs. Multi-variable corelation analysis found renal markers related to cadmium in urine

Propose that 2 µg/g creat in urine should be the maximum tolerated dose - to avoid significant reduction in tubular function i.e. Cd in urine = limit values.....

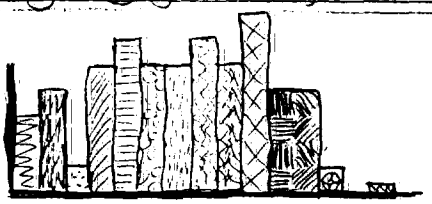
Adult male workers 3 µg/g creat
General population 2 µg/g creat.

Robert Nilsen ? State of health of general population w r t tubular function ?

+

Philippe Grandjean, (Odense Univ. Denmark)

"Mercury: Significance of Intrauterine and postnatal Exposures"



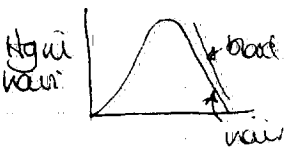
Methyl Mercury only! IRS reviews available very recently

1) Minamata (1953) - release of methyl mercury into Bay = spastic paresis resulting from intra-uterine exposure - Conc of mercury in umbilical cord (Congenital Minimata disease)
umbilical cords kept & dried as figure of good luck ∴ retrospective study allowed analysis of dried cords

2) Iraq Me Hg treated grain used in bread - congenital disease

Iron workers

Hair - ~~Heart~~ to Iraq late 1971 - Hair samples taken -
long strand of hair - each cm represents Me Hg exposure during one month.



Ratio hair:blood ≈ 200
umbilical cord blood much higher than maternal blood (approx 30% higher)
link with umbilical cord levels and maternal hair - reasonable corelation - used data to try and backdate minimata data.

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(~~Coal~~ Correlation mostly in Faroe Islands)
Toxicity can be effected by selenium PCBs and other compounds

~~Most~~ Sources of Mercury? - Volcanic sources -
Probably around half of Mercury burden now comes from human industry

N.B both the cases in Minimata & Iraq were related to subacute exposures. We now, have a real problem with long term ~~chronic~~ chronic mercury exposure in fish eating peoples / mothers.

Breast feeding is there an advantage from breast feeding which is greater than the negative effect of the exposure to Methyl mercury from this route.....

Occurence of Mercury problems world wide.....
Sweden - don't eat the fish!! Greenland - Eskimos - very serious due to high ~~rated~~ rated in diet.....
Canada,
Brazil

George Becking IPCS Human methylation of Mercury - very little evidence

Gwen Silbergeld Courtauld
Mercury in Hair - Pregnancy might affect distribution of Mercury in hair - Poster with reason for concern (see poster p14)

ORGANIC COMPOUNDS

David Ashley: Volatile Organic Compounds Environmental & Occupational (CDC Georgia) Exposure

Exposure assessment:..... Many means but concentrate on blood
VOC exp - Ind, Lab, Env. spill, Occupational = High level
Homes, cars, office, Waste dump sites - common low level

EPA - VOC higher in indoor air than outdoor air - very unusual
= indoor air problem.
Study with active sampling measures -
Proteinadducts - more long term -
Present blood analyses - but only give a very short-term window

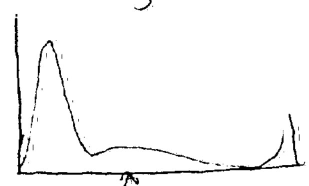
N.B. Vacutainer contamination = major problem in VOCs must be carefully cleaned up.

NHANES III - total 33000 people only ~~6000~~ 1000 for VOCs.

Findings - much intriguing! ....

Peak at Dichlorobenzene low concs - tail off - some higher

Benzene - think bump in tail may be due to smokers - currently doing cotinine.



similarly styrene - smoking well correlated to Benzene.

Pharmacokinetics rapidly lost ∴ must be measured very quickly

Oil Wells Fires Kuwait -

Blood samples from 41 workers within 2hrs compared to NHANES III

Benzene slightly ↑, but others much different

Maine Department of Transport - Printing operation in basement bad ventilation ...... S.B.S.

What 'level' - would you consider a risk?

Dr Christiane Stettler - Chlorinated Dibenzo p-Dioxins + Furans ....
(Zurich, Switzerland)

An issue since Seveso 1976....

Consequences - Dioxin becomes a substitute for all dangerous anthropogenic chemicals

Much misinterpretation .....

Toxicologic properties of all Polychlorinated aromatic compounds - similar
- Hepatotoxic - animal carcinogens - no genotoxicity - No specific teratogenicity
immunotoxicity - latest area ....

1990 WHO arrived at a tolerable daily intake ≏ 10 pg/kg/day

But what about the other congeners 2028541646

Toxicity equivalent factors derived for - Problems because based on animal data which may not apply to humans .... e.g. The half-life data for humans: each varies considerably as then in end of the council is arriving at TDI for TCDD it has to be considered for other cargeners as well. I.e. must be adapted to pharmacokinetic data ...

N.B Avg daily dietary intake in mean at the TDI just from diet etc (100 200 pg TE/day - (10pg TE/kg/d ≈ 600 pg/man/d)

Evidence from Seveso population - No symptoms other than chloracne with very high levels - Even high exp without chloracne ∴ there is probably better than the rat data.

Dr. Staffan Skerving Lund Sweden.

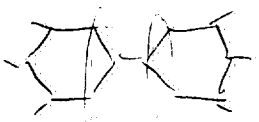
Halogenated Biphenyls: Evaluation of Mixed Compounds & Congeners

Biomarkers of PCB exposure & Risk - & Fr toxic effects of PCBs

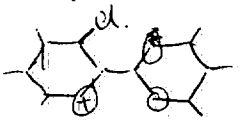
Historically: 1930 Commercial use
1960 Environmental effects
since then restricted use ...

Structure

Non-ortho-PCBs - no chlorine in ortho ⇒ coplanar mol.
No of Chlorines crept for lipid solubility



Nickname here

Mono-ortho  same possibility to coplanar.
No of chlorines also very important

Commercial PCB mixtures:- Aroclor, Clophen, Kanechlor, Phenochlor.
At least 130 congeners in such mixtures ... All mixtures are contaminated with other polychlorin. compounds.

Occupational exposure - in transformer + capacitors - closed
Navally really exposure from accidents

2028541647

Swedish Main problem = environmental contamination.
Dental biomarkers: - Species, Total PB, Mothers etc - - -
Total analysis has several problems

Effects: Cancers; liver effects; immunosuppression; reproductive effects
but always mixed w PCDD's & PCDF's.

Enzyme induction -

Baltic Sea contamination

Poster - Falter & Kutzer. - p62: -

1) Notable that smokers not sig diff from NS in NNN/NNK Hg Adducts
but sig much higher.

2) Rats apparently treated simultaneously i.e. w 500:1 NIC: NNK
showed NIC inhibited NNK metabolism - but was not able
to go higher (ratio in mode > 500:1)
This effect disappeared when given orally. (

3) Dr Elmar Richter: - Results similar to Vallerilla group -
Commented that diffs pbs represent metabolic diffs, may
not be just exposure
Thinks that some explanation in investigating than further
as if it proves to be true then it would suggest that
the TSNAs were less important in LC than previously
thought.

N.S. NHANES III - 30,000 people all tested for cotinine
+ 8 other blood samples etc etc
800 study published in MMWR = planned.
Benzene / Vinyl chloride hope to be linked to smoking
Currently studying potential of Tests explain Cotinine
- perhaps others. - - -
Final data in by Sept 96 but interim data
publication may come out

ROUNDTABLE DISCUSSION ON:-

TOXICOKINETIC ISSUES IN SAMPLING AND INTERPRETATION

N.B. - The main use of hair is to get a long-term measure of internal exposure - for this need

1) little or insignificant external exposure
2) uniform uptake by hair in organic pure chemicals related to blood level
3) stability (no migration in the hair .....

Interpretation - long half-life - what are we measuring these etc etc

Fred Rieders - Nat. Med. serv. Inc. USA

Ethics - we tend to measure because we can not because it can give valuable information.

Backup.

Robert ~~X~~ P81, B25, 2P adducts as markers (IARC)
~~VETS~~, B19 Methodology applied of human milk.
P73 B17 Ethylene Oxide - combined data on all 3 biomarker types
P72 B16 Xenobiotic radical damage in Serum
P71. B15 Complex Pesticide exposure - any solution presented?..
P59. B3 - Micronuclei as markers for pesticide exposure.
P62. B6 - Hb adducts - ?-
P63 B8 - Is this a Biomarker for effect ?- how relate to exp ...
P64 B1 - influence of induction - structure between cancer & exp..
P84 B28 - Benzene in smokers & Passive smokers ? -
P87 B31 - SSB as marker of damage - yes but how specific ?!
P86 B30 - Cat mutagen susceptibility -
P88 - B32 - Premalad biomarkers

Rene Dybkaer, Frederiksberg Denmark.

Quality assurance; Accreditation & certification: Needs & possibilities.

Stan Venitt (ICR, Surrey)

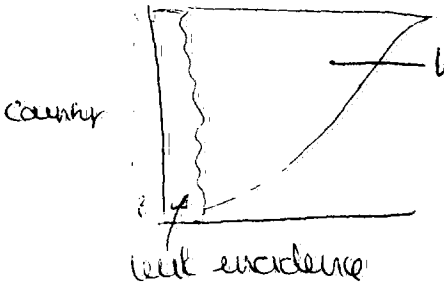
Individual Susceptibility: Relevance to Interpretation

Oncodenes - Knudson - 1986 4 groups 1986

1. Background: Incidence by random mutations in normal people (theoretical)
2. Environmental: exposure to external carcinogen
3. Environmental - genetic: incidence determined by genetic susceptibility to env. car
4. Genetic: genetic susceptibility = most important cancer cannot be cured

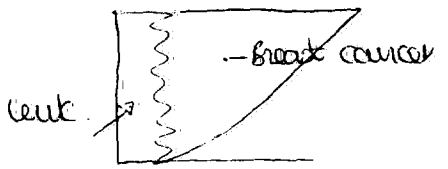
Environmental carcinogenesis - how do you know?

Comparing 2 cancer incidences - leukemia in men.
lung cancer.



suggests that this area is entirely due to smoking (avoidable!!)

Breast cancer v leukemia



i.e. life style important in Breast cancer.

Migrant populations: - Polish born American etc ...

Doll & Peto 1981 Avoidable causes of cancer.

Tobacco = main culprit
Diet - second
} These should be direction of Public Health control.

Effects of genetics - not much evidence that county diffs are due to ethnic differences.

ONCODENES 3 + 4 ③ Environmental - Genetic ④ Genetic.

③ XP + sunlight → skin cancer.

④a) Mutns ⇒ ↑ apart mutn rate (Bloom syndrome)

b) Mutn in "cancer gene" familial adenosis polyposis

Some heritable genes predisposing to cancer

Hereditary non-polyposis colorectal cancer (APC gene) 39 / 2 } group 4 disorders
Breast (17q)
Pituitary ... etc etc ....

Group 3 = more relevant w.r.t susceptibility
e.g. XO, Turners syndrome, Tel At., Bloom's syndrome

Individual susceptibility could appear at any stage of chemical car.

Metabolism
DNA adduct formation
DNA repair etc etc ....

Proto-oncogenes / Tumour suppressor genes / Proof-reading genes *?

Acetylator status - not yet linked to cancer susceptibility.

1. It will soon be possible to develop genotypic predictor assays to cancer (& other diseases)

2) Ex cancer gene - only offer prophylaxis or treatment.

3) abortion? -

4) where prophylaxis or abortion is rejected - going to clinic!!

Weighting polymorphisms may not be straightforward.

Genetic Morality: -

Nicholas Ashford - MIT

Monitoring the Worker: Legal and Ethical considerations ...

Examples of monitoring events that suggest the need for new approaches.

1) ~~Down~~ Cystic ~~Down~~ - Genetic screening of Blacks for sickle-cell trait
2) Love Canal NY - 1
3) Times Beach - Dioxin
4) Woburn MA - leukemia cluster - sick CNS problems etc...
5) PBB's in Michigan - Moral dilemma for nursing mothers

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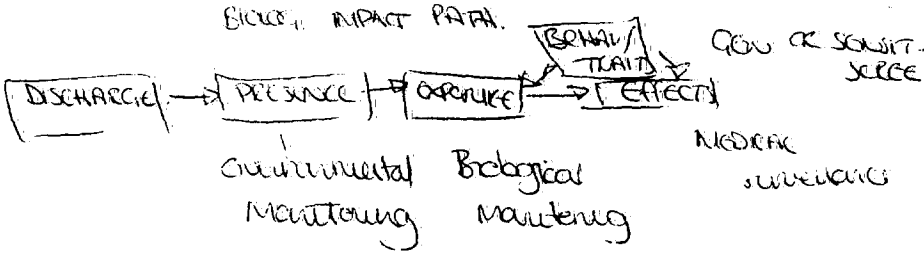

Why do citizens & workers need this information

1) To improve environment as best it.
2) To be alert to past exp for compensation & potential disease development
3) Compensation rates

The right to know - duty to have the information, to obtain it and to disclose it on request or automatically

Factors needed by 1) Scientists for Risk assessment
2) Regulators (with help from scientists) Risk managers
3) Community residents and workers.

What Evidence triggers a requirement for action.

Science - causal inference

Science Policy - interpretation / prudence in prediction

Social Policy.

i.e. standard of scientific proof varies with the political requirements

Political Dilution - May reduce individual risk but depending on the dose response curve could actually increase the total burden on the population.

Potential Conflicts from legitimate diffs of interests between actors/invest.

From Moral & legal responsibilities of Actors / Institutions

From Perception of right & wrong, fair or unfair among the actors / institutions

? You started out with a list of events which 'rang' the alarm bells to decide that something had to be done to provide guidelines of how to act. Do you now consider that the "guidelines" that you are advocating could have been applied to this list and if they had been at that time would the outcome have been more satisfactory?

Friday 18th.

Proof Reading Cards:- Vegetarian Science - Polyploidy 2 papers.
Also Nature article from Pauci ....

Peter Farmer Carcinogen Adducts use in Diagnosis and Risk Assessment.
(MRC Toxicology Survey)

Molecular Dosimetry - assessment of internal dose of a toxic compound by measurement of the extent of chemical interaction of the compound with biological macromolecules e.g. DNA & protein.
But need very sensitive techniques :- Immunoassay
fl. NMR Fluor Spec GC-MS

Poss, 1992 - Lancet Liver cancer & Aflatoxin
Urinary aflatoxin adducts / DNA
Urine N-7(-2-hydroxyethyl)guanine = ethylene oxide adduct ...
DNA carcinogen adduct analysis w ~~P~~ 32P analysis

32P can measure virtually all groups ....

Endogenous free radicals → thymine glycol - in animal DNA found at levels of around 9 - 13/10^6 (Rat liver, Calf Thymus) which is enormous compared to some of exogenous known!!

Where does DNA come from? -
Blood samples / Placenta / Bladder epithelium / respiratory smears

Protein Adducts Not as biologically relevant ....

Haemoglobin (or albumin occasionally)
- readily accessible
- long lifetime of adducts (4 months)

4-aminobiphenyl - cig smoking Tavenbaum 1987
But characteristic finding is that even non-exposed have some exposure evident.

Et Ox - Protein damage compared to other means.

Ubiquity of adducts even in non exposed ....

Biomarkers of DNA damage: SCE, CA, MN, HPRT & HB mutation

Currently looking at non-target site adducts - & possibly non-target adducts.

But is a great gap .... And the evidence relating adducts to human incidence requires much more work ....
Also background so we should be very wary of slight changes (10% background .. < 10% should not be of great extra burden)

Glen Silbergeld ....
All exposed to cigarette smoke - even in newborns - according to CDC data. Thus is highly possible -

But also could be endogenous for methylation ...

Peter Farmer response - dose another on ethylene oxide & point mutations .. does not feel that it is entirely responsible for this - although Hb-AA data may be former!!

Masayuki Ikeda :- Dpt Pub Health Kyoto Japan.

Complex Exposures: Potentials for Assessing Integrated Exposures

Occupational mixed solvent exposure - + food exposures

Ikeda 1983 "The additivity is assumption is safe enough"

The focus should be on the risk of more than additive effects

Hand sorted 21 journals on occupational toxicology from 1983-1991 looking at interaction of materials

NB noted publication bias - Non-significant easily.

Toluene / Benzene exposure in rats

From 159 cases 49 were had more than additive

but 42/49 cases showed technical drawbacks ... uncorrected = 107/111
< additive.

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Renate Kimbrough, Nat. Acad. Natural Hist. Washington. U.S.A

Determining Acceptable Risks: Experimental and Epidemiological Issues

Acute diseases v chronic diseases - May be some difficulty in separating causes - chronic diseases usually wait ages

Risk Assessments: USA Basic assumptions: -

- Dose Response
- Extrapolation to low doses
- Extrap to human
- Not much inter/spp variability

But all these not really valid

Main discussions re lowend of dose-response curve.

- Animal model
- doses
- data interpretation
- uncertainty factors
- threshold - no threshold

Acceptable risk of 1×10^{-6} for carcinogens but much debated

Toxicokinetics - As yet do not consider the toxicokinetics

- metabolites
- tissue distribution
- target organs

} could get more info to make better assessments

Eg. ANIMAL EXTRAPOLATIONS

1. 1,3 Butadiene
   - rat liver has more epoxide hydroxylase
   - use glut-s-t less for elimination
   - epoxyhydroxylase higher in humans

. have to decide which /rat/mouse/ would be a more suitable model for humans - seems that rat will be more sensitive more dose but in fact neither rat nor mouse are good predictor.

eg 2 Methanol Metabolism v different in many spp.

Methanol → formaldehyde → water

Although the mechanism may be diff do not know how it may effect toxicity

Diff in toxicity cause by further formaldehyde metabolism diffs - All animals form formic acid but animals are more capable of coping with the formic acid burden than humans but do not get blindness etc

(= folate dependent pathway more effective in rats than humans - Mechanism is the same but degree diff)

eg. 3 TCDD.....

Not sufficiently examined affinity for liver binding sites for diff spp. Some evidence of diffs between rat strains Some studies in Canada on receptor in humans that suggests AH receptor in humans binds TCDD less tightly than animals which may effect distribution

Also appear to be some distribution differences between Rats and humans in laboratory tests

Sampling, sampling collection & specimen analyses - should work more closely together chemists & toxicologists--

Indirect measures - division between biomarkers of exposure and biomarkers of effect

Chromosome aberrations have caused - nothing known about health consequences

THIS IS NOT TRUE.

Smokers - cannot tell individual risk even if overall risk known

Cholesterol - elevated levels may ↑ Heart risk but we don't have enough good evidence that cholesterol reduction will help

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In addition to disease progression can have regression & repair

adaptation - Very little work in area of reversibility -
— THIS ALSO IS UNTRUE —

Background levels have to be well established before risks are assessed - otherwise false alarms can be raised.

Health significance of early changes: Enzyme induction
Macromolecular alkylation
Chromosomal Changes
Blood Chemistry
Immunological Response
Neurobehavioural functions

Concludes examples.....

* NO MENTION OF RISK ASSESSMENT FROM EPIDEMIOLOGICAL STUDIES... *

What does EC think of primary cultures...? - in some cases can be appropriate but devoid of "normal" background

Stoffanstörung - as regards CA in study with follow-up of cancer
Lund, Sweden is now a significant increase in 3rd of cohort with the highest levels of CA.
SCE - no significant results. Cohort study
Can we 'link' individuals...?

86 guidelines of carcinogenic Risk assessment in F.R for TPA
said when we have pharmacokinetic data we must use it.

2028541657

ACTION LEVELS: Definition and Use.

Ann Robinson – IPCS Geneva Switzerland

Advice for Risk Manager.

Current "Action levels"

Administrative burdens – basis to prevent health effects ...

Action level should protect all or most of subjects

Political // Scientific boundaries

WHO/IPCS approach: hazard identification
Dose response
Exposure assessment
} Assessment.
"Risk characterisation"
= Risk communication
Risk Management.
(Social cultural elements)

Conclusions – Scientific judgement has to provide information to politicians to make decisions
but no decision is definitive

Toxicology is not an isolated science in this respect.
In spelling out the risks and hazards of chemical the risk manager has to understand all the possible consequences of change – e.g. Pb & Petrol
Consequences health & economics

—

Concluding Remarks:-

The Ideal Biomarker: – Simple collection & analysis
– Clear relation to exposure & effect/Risk.
– Subclinical & reversible effects
– Intervention/prevention should be possible
– Ethically acceptable

Very far from achieving these goals but they should be kept in mind.

2028541658

VALIDITY OF BIOMARKERS:-

- Analytical – (crucial) ... precision with
- Toxicokinetic / Pathogenetic
- Diagnostic (+ specificity etc)

APPLICATION OF BIOMARKERS:-

- Research exposure → Dose
  Dose → Effect / Response.
- Individual Diagnosis / Risk prediction
- Assessment of Compliance / Effect of prevention.

Next Conference - NICE 1995

To do Monday 21st

1) See HGR about an Agenda for Tuesday.
   Are we supposed to be doing the Public cost of smoking? . . .
   If so trace that reference - also ask Mitch Re what he has . . . -
2) Copies of TAC papers to be put on stairs

TAC: 22nd June 1993.

Emerging Issues Meeting:

Chris Bullock leaving at end of July....
Scientific issues reducing in significance - TAC should only be involved in scientific issues relevant to trading issues. = umbrella organisation.
Work to be done through alternative inter company arrangements.
TAC should be properly briefed on scientific issues likely to come into the public affairs arena. ...

Ad Hoc issues - steering committee made up of Senior Scientific Managers from all the companies.

RET:
"Safety net" objective -
Should not restrict ourselves only to TPRT studies - are many other relevant studies....

"Junk Science" Seminar - Chaired by James Le Fanu.
Emerging Issues group should be there to develop means of using the science.

BO'N - Who/what are our targets? Individual scientists; government/regulatory authorities etc?

AJN = Linkman between TAC & Industry scientists

David Swan -
Is there/are there any factors which we can adopt in the U.K. to "discredit Junk Science".....
e.g. Junk Science seminar with gavernment sub-committee & James Le Fanu....
To think about for future reference.
To come up with something by end of July?....
Trying to cut down legal costs - get company lawyers to clear things

---

TAC Informational Services - PAS working paper to recommend maintainable information service not duplicated by TDC

come from another source - Rothmans?
Computer system being redefined.
3-4 months should decide what services TAC can offer re information

3) SUBSTANCE USE. Knail Sinclair

David Warburton Support → 1988 Addiction response
Term "Substance use" dangerously close to Heroine.
⇒ ARISE to influence scientists and Public opinion - 2 meetings Florence ⇒ "addiction controversies". Venice meeting - Pleasurable substances
Book shortly to emerge.
3rd meeting Brussels, September. Pleasure and Quality of life.
Thus progressing to lifestyle / Quality of life arguments.
Research program with Dwaio.... concept of craving - forthcoming papers:-
Brit. J. Addict - to come out on concept of Addiction - survey of cessation
and only 6% craving. others said "fancied" cigarette.

Addict. Research. Attribution of symptoms after & before cessation - symptoms
dont change but
J. Psychopharmacology - Nicotine issue - Robinson & Pritchard paper much response
& correspondence on this paper.

Health and lifestyle survey - 9,000 questionnaire survey Wicklow
publications - Warburton showed different diet & lifestyle than
non smokers
Also those people who live with smokers have poorer diet.....
Referee asked to strengthen issue re children living with smokers
PN Lee also analysed same database & calculated cumulative risk
factors could go up to about 2.0 ∴ could represent a clustering of ~~ETS~~
confounders and not ETS.
British Journal of Nutrition.
McGill conference - July 1994 - probably fairly anti - funding (21-24 July 1994)
5) Nicotine Replacement Therapy - CAR, (ITL)
3 month supply in all countries = approx 2X 3 month supply cigs (1000)
Ciba-Geigy largest suppliers - PMI to diversify into other markets

2028541661

'92 920,000,000 $

'93 350,000,000 $ estimate

But effect on market - only around 1-3 % 25% smokers considered using them!

Success of patches trials - % of not smoking from 6-24 months not that much higher than placebo.... 17% highest - 12% placebo.

Nicotine patches represent a cigarette alternative which may take key role in further Health scares.

N.B. also focus on side-effects of nicotine may pressurise reduction of nicotine content in cigarettes.

U.K. pressure on physicians to run smoking cessation clinics.

CECCM conclusion - probably do nothing....

TPRT research at Leicester on nicotine look into before meeting

Colin Cano - development of model for atherosclerosis - plaque formation etc seeing if nicotine has an effect of arteries.

5) Molecular Epidemiology

BAT supports outside groups in molecular epidemiology.....

To acquire knowledge that company could react to and be aware of developments in the science. - Exaggerated claims etc. -

Individual variability Genotype ⇒ Phenotype diffs.

a) Biomarkers for TSNA's - a little under - DNA adducts importance of claims in this area

BP adducts 32P David Phillips survey

Peter Farmer DNA adducts at 10^6 :. shouldn't be concerned about anything else..

Hecks group - methyl group much greater potential than bulky adducts

Adducts in urine - NS exposed to TSNA's.

National Health foundation

Carcinogenesis paper - Deutsch in Switzerland - balance from chemicals which form DNA adducts & smoking

P53 gene mutation - Linda Budge :-

Claims that G→T transversions are from BaP in tobacco smoke.

Reggerie et al PNAS, 90: 1013. (1993) Mice skin painting studies likely to be used in Tobacco litigation claims.

2028541662

- It is not reasonable to blame 15% of potential mutation types on cigarette smoke.

Prof Schwarz on Biomarkers - various pt mutations in ^{32}P - BaP binding to DNA in lung cancer.

RET questionnaire - will send out to us - link with lifestyle factors.

6) Cigarette Ignition Propensity - as read

7) Benzene - COM - to look at combination of diet & smoking.

NHANES IV Benzene survey

Wednesday 23rd June.

1) Meeting J-BB.
2) Check through 'In Tray'
3) Notes' compile all activities required w deadlines....!
   * Unions meeting - prepare answers of research sponsored in areas - see HSE.
   * TAC 15th July Meeting PM poster
   * Benefit of Childhood.... + list of 'potential" consultants - recommended researcher
   * Development plan with HSE.
   * Meeting reports ICC Munich. Brussels conference?
   * Targets/goals Q3 14 1993.
   * TAC work:- Meeting notes/organisation from today?....
   * Ring Mayada Logue about Helsinki trip ..... too late!!

2028541663

23/06/93.

ESMERT..... Ref 167/es3/9185

Article from the Independent, 15th June 1993 - p3.
between 1991 - 1992 Cot deaths fell by 50% to 456 deaths
60-75% of babies who died from cot death have mothers who smoke.
HEA - new guidelines on smoking during pregnancy claim that babies born to smoking mothers are twice as likely to be born prematurely and to be an average of 200g lighter.

Tony Addrade

Addrain case ruled in our favour.

ADA - What research relating to ETS at Unbyte
Have some presentation for awareness - how it might cut w.r.t. legal issues.
Documentation awareness handling & processing documentation
Burial body plans.

Cotinine levels - very low levels re Dioxins etc - "Dangers" associated.
1) irrelevance of detecting v. low levels of any compounds
2) & lack of ability to determine actual source.....
Bring → other egs -
3) Other argument of measure low levels - not related ETS.....
What else may be measured in blood.

EEMA asked 3-4 weeks ago.....

—H—

Phone John Conrad: 00 44 71 333 4793 ex 4789 direct 81 961 3851 home.
- Answer phone - left message will try again tomorrow.

John Warren: 00 46 8 729 49 47. - No answer.

2028541664

Bob Pages - Media portrait EPA out very favourably -

Addiction issue - no great news small claims court : no lawyers
Vanken - call Richard Nancy Jensen has just

Same papers in literature - conflicting results of benzene in serum smokers & nonsmokers - Italian group 1989 & previous - data on

Charlie Green - Reynolds - Mass spec conf in south few weeks ago with CDC - Scientists said very unusual for preliminary data but was political reason
Few weeks after EPA.

-#-

Carrington Quotes (from Chris Proctor?) .....
From Developments in the Science of ETS (from C&B to HER)
May 18th 1993: -

Hazleton study on ETS exposure (for CIAR..?) 250 people in NE England. Misclassification.
"The EPA claimed that (misclassification) happens in only 1% of cases, and adjusted their analysis accordingly. The Hazleton study reports up to 16% of the subjects said that they were non-smokers, but were found actually to be smokers. Should this rate be applied to the EPA analysis, rather than the EPA's assumption of 1%, the slightly elevated overall increased risk of lung cancer reported by the EPA would disappear entirely."

-+-

Japanese study at Teikyo University 400 Japanese women showed smoking status irrelevant to ETS exposure...".
p8. Tokyo conference conclusion from Dr H. Kasuga... No evid ETS.
"In general, though, it seems that the epidemiologic database as it stands today does not support an association between ETS and lung cancer. The workplace data reports no elevation in risk or an increase that is so small that it can be entirely accounted for by bias & confounding factors that have not been properly addressed...".
p9 Dr Luik Quote..." The only reason people who make public policy

turn to science is because they see it as an objective means of arriving at the factual determinations that allow legitimate public policy to be made.....

—ǁ—

June 25th:-

By Monday:-

Childhood Review

Write-up Munich / IAG

Write to Odd

Ring John Warren

Ring John Govod

Ring Max Weetman

In info preparation - past/current ETS studies elsewhere.

Position paper measuring low levels.....

Ring DJC.

Ring Robin Fielder

—ǁ—

Staff Meeting 25th.

Copy to everyone .. of Pregnancy & ETS review..... *

Childhood - ~~dead~~ physical development:- Review / SES dietary

limited - Secondary confounder

Biostatistical approach.... Galway -

any access to WHO

Find out possibility - re Galway/ *

Kids no recommendation to do likewise - more biostatistical

Leading Prof. in Institute Vet him!

—ǁ—

SIDS: IAM Centre on SIDS in France -

To do more homework.

2028541666

Source of information before publication French - not worthwhile.

And - search on "smoke" exposures - find out what's in the literature.

Coordination with Mitch re Calway / Waxbuster substance abuse . . . .

Ring Odd Nilsen Monday! (or send a fax?)

Ring Richard ~~Monday~~ Tuesday response to Manny's request.

Leave note/message with Jill for contact at home.

Wiley - in vitro.

Smoking machine under positive pressure - puff created by 'normal' pressure
deviations from ISO:- greater variance
rectangular curve

Burley pH increases w puff no. } NNK in burley much
Flue pH decreases w puff no. } higher than flue.

NB "pH" ≠ real pH

Could the pH thus explain ↑ in NNK values?
Oriental tobacco very low in TSNA's.

Biggit — Publication from Japanese circumstancies in:- No of hairs (hence detect. limit)
C3H/S-6 v. = 100.

- Rat dose 3ng/kg/day
in vitro = 20ng/kg/day
but plasma equivalent!
- claim v. little effect of external in vitro urine opposite

Re tar cytotoxicity etc - could it be included that if exposure to ETS is measured by TPM - related to No of cigarette equivalents - could compare cytotoxicity on a UX/ETS basis.

Definition of boundaries in "market place" re biological activities

HERC - VOC activities w ETS....
Affa Magnussan - Childhood ETS exposure

RR - Current trends:-
ATS meeting Trickle of animal & epidemiological studies - except cardiovascular studies no change CV. v. dog increasing likely to be a risk in the studies
probably w negative studies following (cf. old Fusion)
Loemberger study Switzerland showed strongest relationship w workplace which is contrast to other studies on exposure - chronic
Radon studies Sweden - ETS data also included results probably in fall.
Biases in literature re the results
In a review of expt/epid studies logistic difficulties in interpretation
Agent → dose → effect (clinical)
→ (urinal!)

2028541668

Hormeris - more frequently expected! - could be related to CST data on smoke exposure.

Could we use mouse skin painting to see this - i.e. go down to very low levels of SS condensate with & without another (weak) carcinogen to see if low SS might reduce tumours obtained when carcinogen applied w/out ~~&~~ SS.

Scientifically intervention studies are most useful/important in confirming or otherwise epidemiological findings but little known by public.

Coronary Heart disease and smoking.

Socio-economic class most important for nutritional & dietary factors.

e.g. Rodon study found risk higher among smokers but no dose response effect with respect to N° of cigarettes smoked - likely to be due to some other factors - e.g. lack of protective factors in disease.

- Areas which should be explored ∴ should look more actively for alternative ~~reasons~~ explanations/factors.

Kentucky meeting when fat taken into consideration CHD risk ↓ almost to zero

Magnesium - similar extent to active smoking in drinking water

- NB. alcohol also increases magnesium.

Confounder study at CIIR - approved - should be design out soon.

Atherosclerosis studies in Rabbits -

- Uterine exposure. Canada study in Kentucky on teratogenicity - ongoing. In line with OECD guidelines.

High dose 2 µg/l low dose 0.5 µg/l (= lowest dose of BASS which can be consistently found)

25 ng/kg = 1 µg/l on 6h basis

100 ng/l on 6h basis ∴ 2 µg/l = 80x.

2028541669

John Wahren - 00 46 8 729 4947
sec. - 00 46 8 729 37 78
FAX - 0046 8 329 022
John Conrod :- 0044 71 351 2488
Private 0044 81 861 3751
FAX. 0044 71 351 5307
Max Weetman :- 00 44 91 515 2603 (office)
00 44 91 415 409 (Home)
FAX. 00 44 91 415 7778

John Conrod | received cheque for books ready to be produced
£200 ⇒ check as soon as possible - BAT -
CIBA-GEIGY
[£500 - guaranteed -

* Good idea to put in writing to change invoices to Peter. *
check situation - get letter

Turkey in 15 min factory - ?'s about industry =
mixed with don't know ⇒ most only
work could be done jointly with Turkey & UK
(new person - not urgent) in Ankara - Antalia -
lady Dr Semra ~~[illegible]~~ Kovucu University of Ankara -
person involved in research nitrosamines etc but more basic
things & urine metabolites risks diff from europeans / rabbits
excretion? - "British Council" also interested in Turkey
funny ratio of metabolites most common N-oxide ≈ 2/3
but some genetic discarded ⇒ 100:1
but never extended to other ethnic groups ! - doctors link
at all 's blood data = No PhD - more high-level technician
or post doc ⇒ statistician could be available - PhD
funding finished ⇒ New potential TTC data want to go Bristol 4-
all set up really cost of salary + achieved + consumables, £30,000/y
(probably 1 year)

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PRIORITIES

Draft letter to JA CO round all projects re change of Peter leaving and myself taking over.....

Ruig John Wansen.

Targets? - pesticide Toxicology & regulatory status & background.
- zero threshold.
- presentation tools - compatible w associates - powerpoint
- carcinogen classification - worldwide & European
- Review all animal studies } as ETS/SS
& all in vitro studies }

- SE Directors
- childhood parts in prep for SG report
- Health effects of early initiation? - re SG report what are consequences of this

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